

DETERMINANTS OF PATENTING IN THE U.S. PHARMACEUTICAL INDUSTRY

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This paper examines the patenting behavior of both generic and brand¹ pharmaceutical industries, determinants of the patenting strategies used by the pharmaceutical industry, and how incentives to patent have changed and are changing as a result of recent CAFC decisions² and legislation.

Life cycle management of pharmaceuticals involves a wide range of patents that may be obtained before, as well as after, approval of a new drug. Evidence suggests that the pharmaceutical industry relies heavily on patent protection to recoup R&D investments, despite the tremendous growth of generic drugs.³ A company may have a great deal riding on one drug and, consequently the pharmaceutical industry has become increasingly litigious because of the stakes involved. A number of vexing issues regarding pharmaceutical patent protection have arisen in the litigation context. Recent Court of Appeals of the Federal Circuit (hereinafter CAFC)⁴ decisions and resulting legislative changes involving patents on metabolites, polymorphs, purity, off-label uses,

¹ Throughout this manuscript, new drugs are referred to as “brand” drugs, although they are also frequently referred to as “innovator drugs” or “pioneer drugs.”

² Pharmaceutical patent cases begin in District Court and then go to the Court of Appeals.

³ See THE 1994 CARNEGIE-MELLON SURVEY OF INTERNATIONAL R & D. The Carnegie-Mellon Survey found that patents were an effective way to capture returns from R&D dollars for a handful of industries only (e.g. pharmaceutical, chemical, medical device); see also M.A. Lemley, *The Economics of Improvement in Intellectual Property Law*, 75 TEXAS L.R. 989, 1084 (1997); R.C. Levin, A.K. Klevorick, R.R. Nelson et. al., *Appropriating the Returns From Industrial Research and Development*, 3 BROOKINGS PAPER ON ECONOMIC ACTIVITY 793, 820 (1987); R.P. Merges and R.R. Nelson, *On the Complex Economics of Patent Scope*, 90 COLUMBIA L.R. 839, 916 (1990).

⁴ In 1982, the Court of Appeals of the Federal Circuit, a centralized appellate court with jurisdiction over all patent infringement appeals was created to encourage uniformity among US courts in interpreting the patent statute. Creation of the Federal Circuit strengthened patent rights by establishing various procedural and substantive rules that made it more difficult to challenge a patent’s validity, increased penalties on infringers by awarding higher damages and increased the likelihood of the grant of injunctions against infringers. The “clear and convincing evidentiary standard” established by the court increased the burden on challengers seeking to invalidate a patent owner’s rights; see generally H.W. Nies, *Ten Years of Patent Law Development Under the US. Court of Appeals for the Federal Circuit*, 24 IIC 797, 803 (1993).

dosing regimens and “submarine” patents have important ramifications on the patenting of pharmaceuticals.

I. INTRODUCTION

A. The Current Situation

Fundamental changes in the United States pharmaceutical industry during the past decade have reshaped how firms protect and enforce their intellectual property rights. In bygone days, there was typically a ten-year development and regulatory approval process, the drug was then sold until the day the patent expired, at which time it was handed over gracefully to the generic companies.

Patent rights are inherently a right to exclude. A patent gives an inventor the rights to exclude others from making, using and selling the invention for a limited term, 20 years from the application filing date in most of the world.⁵ The primary goal of patenting is protection of the firm’s competitive advantage from product or process innovation. By 2006, almost 200 patents covering \$36 billion in pharmaceutical sales will expire. Pharmaceutical products have a relatively short product life cycles and competitive advantage is largely driven by lead time.⁶ The typical remaining life of a drug patent that has undergone Food and Drug Administration (hereinafter FDA) review

⁵ See U.S.C. §154. The twenty year term is a relatively recent development, with the purpose of conforming U.S. patent law to international standards; see also Pub. L. No. 103-465, §532, 108 Stat. 4809 (1994) (codified at 35 U.S.C. §154(c)(1)).

⁶ Patents provide protection for 20 years from the date of patent filing. However, this applies to applications filed on or after June 8, 1995. For applications filed before June 8, 1995, the expiration is 17 years from issue or 20 years from filing, whichever is longer.

is on the order of approximately 10 to 12 years.⁷ Most articulations of the value of patents in the pharmaceutical industry today presumes patents not only provide protection for a pharmaceutical product or method of manufacturing, but now enjoy broader “strategic” use that enable the firms to avoid being excluded in a particular field of use, to obtain favorable terms to their licensing agreements, and to safeguard against costly patent litigation.

This broader “strategic use” of pharmaceutical patents manifests (1) in the creation of in-house “patent committees” to oversee, and simplify, the process of writing, filing and revising patent applications, and (2) the hiring of more in-house patent attorneys, elevating the role of patent attorneys within the firm, and expanding their involvement in corporate activities such as strategic alliances, licensing and litigation decisions.

However, there are still different interests in patenting by brand and generic pharmaceutical companies and these differences manifest themselves in different patenting strategies. For generic manufacturers patents are a means to generate capital to fund research, whereas for brand manufacturers, patents are not a means for raising capital but simply a means for ensuring an effective commercial monopoly for their products. Patenting strategies that work for brand manufacturers could be disastrous for generic manufacturers.

⁷ Joseph DiMasi, Presentation on Drug Development and the Effective Patent Life Since Enactment of the Hatch-Waxman Act, The Center for the Study of Drug Development, Tufts University, 1999; *see* Kenneth I. Kaitin, IMPACT OF THE PRESCRIPTION DRUG USER FEE ACT OF 1992 ON THE SPEED OF NEW DRUG DEVELOPMENT, Tufts Center for the Study of Drug Development, prepared for the FDA Public Hearing on the Prescription Drug User Fee Act (Sept. 2000).

Brand and generic pharmaceutical manufacturers are as often litigants against one another as they are partners in strategic alliances. This dichotomy between generic and brand pharmaceutical manufacturers currently characterizes the pharmaceutical industry. Sometimes the lawsuits become extremely intense and litigants refuse to reasonably cooperate in expediting the action.⁸

In 2002, the FDA approved 321 generic drugs.⁹ Once the patent of a brand drug expires, genericization is rapid.¹⁰ Despite promising pipelines, a company may have a great deal riding on one drug where the company has constructed a platform for global launches and branding. These circumstances have spawned brand industry attempts to use the legal system to find loopholes to extend their patents. Under the Hatch Waxman Amendment,¹¹ generic manufacturers not satisfied with waiting until patents expire have the option of trying to prove that an existing patent is invalid. The mechanism for this challenge is a paragraph IV certification.¹² A generic company that successfully

⁸ See *Andrx v. Biovail Corp.*, 61 U.S.P.Q. 1414 (Feb. 11, 2002) where the court reversed the District Court's shortening of the 30 month stay based on alleged conduct in FDA proceedings. The 30 month stay may, however, be shortened pursuant to 21 U.S.C. §355(j)(5)(B)(iii) if a party to an action fails to reasonably cooperate.

⁹ Of those, 80 were first time generics. The FDA also issued 63 "tentative approvals" and 20 "approvables". A tentative approval indicates that final approval of the application is delayed due to patent or exclusivity issues. Approvable applications are reviewed and ready for full approval pending a labeling issue, also typically dealing with legal matters.

¹⁰ Generics must meet the same standards for manufacturing, identity, strength, quality, and purity. Minor differences in labeling are allowed to account to manufacturer-specific modifications such as tablet shape, color, etc.

¹¹ Pub. L. No. 98-417, 98 Stat. 1585 (codified in scattered sections of 15 U.S.C., 28 U.S.C., 35 U.S.C. (1994)). Also known as the Drug Price Competition and Patent Term Restoration Act.

¹² In a paragraph IV certification, the generic manufacturer asserts that patents listed in the Orange Book will either (a) not be infringed by the making, using, or selling of the proposed generic product or (b) will be invalid and or unenforceable if the claims are asserted to encompass the generic proposed products. In a paragraph IV certification the generic company must supply specific reasons to support these statements, e.g., proposed product has a different dissolution profile than that claimed.

challenges a patent is allowed six months of exclusivity.¹³ Once a paragraph IV certification is filed with the FDA, brand companies have a 45 day time period with which to sue. There is an incentive for brand companies to sue because even if the lawsuit is unsuccessful, the generic versions are kept off the market for months.¹⁴ This results in a *de facto* extension on the length of the patent term.¹⁵

B. Overview of Hatch-Waxman Provisions

Title I of the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch Waxman Amendment, specifically authorizes Abbreviated New Drug Applications or ANDAs under section 505(j) and 505(b)(2) applications.¹⁶ A 505(b)(2) application seeks approval of a new drug but at least some of the safety and efficacy data relied upon comes from studies conducted by third parties, not by, or on behalf of the applicant.¹⁷ This section also provides for five years of

¹³ See 21 C.F.R. §314. The exclusivity begins either when the patent infringement suit is fully adjudicated or upon marketing of the generic product.

¹⁴ In some cases this means hundreds of millions of dollars in sales. *But see* Bethany McLean, *Prozac, A Bitter Pill*, FORTUNE, August 13, 2001, at 4. There is also an incentive by some generic companies to attract an infringement suit, and get “paid-off” in a settlement, never intending to market a drug.

¹⁵ See FDA, GUIDANCE FOR INDUSTRY ON COURT DECISIONS, ANDA APPROVALS, AND 180 DAY EXCLUSIVITY UNDER THE WAXMAN-HATCH AMENDMENTS TO THE FDCA, 65 Fed. Reg. 16, 922-23 (2000).

¹⁶ FDA, Abbreviated New Drug Application Regulations: Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,358 (Oct. 3, 1994). While drugs marketed before 1938 were initially exempt from the NDA process, any new dosage form of these chemicals constitutes a new drug. A number of grandfathered drugs marketed before 1938 are included in the Orange Book, and as such have gone through the FDA approval process and have bioequivalence data.

¹⁷ Recently, Citizens Petitions were filed by two pharmaceutical companies and a biotechnology industry group challenging FDA’s interpretation of Section 505(b)(2) of the Federal Food Drug & Cosmetic Act. FDA has stood by its interpretation. The FDA response letter to the Citizen’s Petitions is available at <http://www.fda.gov/cder/ond/505b2-cpresponse.pdf>.

exclusivity for New Molecular Entities.¹⁸ Once a New Molecular Entity is approved, a generic version cannot be approved for 5 years.¹⁹ There is also a three year exclusivity for changes requiring NDA or supplemental NDAs such as line extensions, a new use or indication, new salt or ester, for marketing a drug over the counter, or a new strength requiring clinical trials.²⁰ An ANDA may be submitted but may not be approved if the ANDA contains the change for which exclusivity was granted. That is, no ANDA filings are permitted until the end of the new chemical exclusivity period and no ANDA filings are approved until the end of the clinical exclusivity period. Effective exclusivity is even longer than five years for new chemical entities since approval of ANDA applications averages over 30 months.²¹

When an ANDA is filed for a generic version with bioavailability data, one of four certifications must be made: 1) that the drug has not been patented, 2) that the patent has already expired, 3) the date on which the patent will expire, and that the generic drug will not be marketed until that date passes, or 4) that the patent is not infringed, is unenforceable, or is invalid.²² These certifications are now referred to as Paragraph I, II,

¹⁸ Also referred to as “new chemical entity” or “NCE”.

¹⁹ The only exception being if a patent is also listed on the NDA product subject to NME exclusivity, the FDA may accept an ANDA after 4 of the 5 year period has expired, if the ANDA contains a Paragraph IV certification. There may also be situations where multiple NDAs are approved for a single drug product and a product not designated as the reference listed drug is actually shielded from generic competition. There is a process that allows a firm wanting to market a generic version of such a drug to do so. Therefore, in some situations there may be several reference listed drugs.

²⁰ However, the exclusivity is only for that new indication or dosage form. There is also a 6 month exclusivity for pediatric testing and a seven year Orphan Drug exclusivity but these provisions are not part of the Hatch-Waxman Act.

²¹ See *Glaxo Inc. v. Novopharm, Ltd.*, 110 F. 3d 1562, 1568 (Fed. Cir. 1997) (describing the legislation as “designed to benefit makers of generic drugs, research-based pharmaceutical companies, and not incidentally the public”); see also *Eli Lilly & Co. v. Medtronic*, 496 U.S. 661, 672 (1990).

III, and IV certifications. There is also a “little viii” statement (also known as a “statement of inapplicable use”) reserved for patents covering the use of a drug listed in the Orange Book. Applicants file a “little viii” statement that the generic labeling does not include the patented use.²³ A generic drug receives 180 days of exclusivity if it is the first to file a complete ANDA containing a Paragraph IV certification during which time no other generic companies may enter the market.²⁴

Under Hatch-Waxman, patent extensions are permitted to compensate brand companies for time spent in the regulatory approval process.²⁵ Title II, the patent term restoration part of Hatch-Waxman is extremely important to brand manufacturers because the U.S. patent usually issues long before clinical trials begin on the compound and in the U.S. the twenty year patent term runs from the time of filing the patent. A pioneer receives a patent extension term equal to half of the time of the IND period (time from when the IND becomes effective through NDA submission) plus the time for NDA review. The patent term extensions are for a maximum of five years, in addition to the initial patent term.²⁶ Additionally, the remaining patent plus extension cannot exceed 14 years, regardless of how much time was lost due to clinical testing and review. Only one

²² 21 U.S.C. §355(j)(2)(A)(vii)(I)-(IV) and implementing regulations 21 C.F.R. 314.94(A)(12)(i). A paragraph I certification is appropriate when there are no patents listed in the Orange Book. A paragraph II certification is appropriate when there is a patent listed in the Orange Book, but it has expired. A paragraph III certification is appropriate where the ANDA applicant intends to “wait out” the patent until expiration. A notice of a paragraph IV certification must be provided to each owner of the patent that is the subject of the certification and to the holder of the approved NDA to which the ANDA refers.

²³ Section viii statements require no notice to the patent holder, nor do they trigger a 30 month stay of approval.

²⁴ FDA has used either a District Court or an Appeals Court decision to begin the start of the 180 day clock.

²⁵ Market exclusivity and patent protection may run concurrently.

²⁶ See 35 U.S.C. §154 (1994).

patent may be extended per regulatory review period.²⁷ Further extensions are not available for different dosages or drugs containing salts of the same active ingredient.²⁸ Patents covering method of use, method of manufacturing, and products are eligible for patent extensions.²⁹ Other limitations include that the extension is limited to approved use; the term must not have been previously extended; the extension applies only to the first marketing or use of a new active ingredient.

Legislative patent extensions for specific pharmaceuticals have occurred in rare instances where there are some extenuating circumstances that resulted in a substantial loss of the benefit of the patent term.³⁰

After the FDA approves an NDA, the patent information will be published in Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known

²⁷ See Terry S. Colman, *Waxman-Hatch Exclusivity Provisions Not Related to Patent Status*, 46 FOOD DRUG COSM. L. J. If a manufacturer holds both formulation and method of manufacturing patents, the applicant must choose one for patent restoration.

²⁸ See *Fisons PLC v. Quigg*, 8 U.S.P.Q. 2d 1491 (D.D.C. 1988), *aff'd*, 876 F. 2d 99 (D.C. Cir. 1989) (interpreting “product” to refer to the drug’s active ingredient; *but see* *Pfizer Inc. v. Dr. Reddy Laboratories, Ltd.*, Fed. Cir., No. 03-1227, Feb. 27, 2004 where the U.S. Court of Appeals for the Federal Circuit defined drug product as “any salt or ester” of the active ingredient, holding that a patent term extension for amlodipine covered both the besylate and maleate salts. Dr. Reddy, which filed an NDA under 21 U.S.C. § 355(b)(2) sought to market amlodipine as the maleate salt, arguing that although Pfizer’s patent covers additional salts, Norvasc[®] or the besylate salt was the registered product entitled to the patent term extension (effectively changing the law in this area); *see generally* Suzan Kucukarsian & Jacqueline Cole, *Patent Term Extension Under the Drug Price Competition and Patent Term Restoration Act of 1984*, 49 FOOD & DRUG L.J. 511, 522 (1994) (analyzing the patent extensions under Waxman-Hatch up until late 1994); Edward Hore, *A Comparison of United States and Canadian Laws as They Affect Generic Pharmaceutical Market Entry*, 55 FOOD DRUG L.J. 375 (2000) (describing the U.S. laws pertaining to generic pharmaceutical market entry). *Pfizer Wins Appeal on Generic Norvasc: All Salt Claims Extendable*, PHARM. LAW & INDUST RPT, Vol. 2, No. 10 at 253, March 5, 2004.

²⁹ 35 U.S.C. §156. Drug products are statutorily defined and include biologics and-antibiotics. Patents covering PMA medical devices, new animal drugs and veterinary biological products may also be extended. *See* Kevin J. McGough, *Preserving the Compromise: The Plain Meaning of Waxman-Hatch Market Exclusivity*, 45 FOOD DRUG COSM. L.J. 487,487 (1990); *see generally* Donald O. Beers, *GENERIC AND INNOVATOR DRUGS, A GUIDE TO FDA APPROVAL REQUIREMENTS*, §4.04[D] (5th Ed. 1999) (for help in understanding the calculation of patent term extensions). Hatch-Waxman exclusivity is not related to patent status.

³⁰ *See* Richard M. Cooper, *Legislative Patent Extensions*, 48 FOOD & DRUG L.J. 59, 63 (1993).

as the “Orange Book” due to its orange colored cover.³¹ The NDA holder may list multiple patents that claim the approved drug or an approved method of using the drug product.³² Each may have a different expiration date and offer its own unique protection to the NDA product.³³ Even though the list of brand drugs and the dates that their patents expire is publicly available in the “Orange Book”, the list is inconclusive as there currently is no way to tell which of these drugs will actually go off patent.³⁴

The intersection between Hatch-Waxman and patent laws has spawned a great deal of litigation involving “Orange Book” patents, mostly in the area of paragraph IV certifications. If a generic company files a paragraph IV certification, it must notify the patent holder, who has 45 days in which to file an infringement action³⁵ and then there is a 30 month stay before an ANDA can be approved (unless there is a final appellate decision³⁶ earlier which is very rare; also if the patent runs out in that 30 month period, the lawsuit becomes moot).³⁷

³¹ Should a patent issue during the FDA’s review of the application, the NDA holder is required to amend the application with the new patent information. For patents granted after FDA approval, the NDA holder is required to submit information on the new patent to the FDA within 30 days of patent issuance. *See generally* 21 U.S.C. §355(c)(2).

³² *See* 21 C.F.R. §314.53(d)(3). If the patent could not have been submitted with the NDA, as e.g., when it did not issue prior to FDA approval, the NDA applicant must provide the patent information to the FDA within 30 days after the patent issues.

³³ 21 C.F.R. §314.53(b) (pertaining to patent listing requirements for NDAs).

³⁴ The Orange Book is available at the FDA web site at www.fda.gov/cder/ob/default.htm. The Orange Book is also known as Approved Drug Products With Therapeutic Equivalence Evaluations. Process patents are specifically not required to be listed.

³⁵ *See* 21 U.S.C. §355(j)(5)(B)(iii); *see also* 21 U.S.C. § 505(b)(3)(a) (providing that an ANDA applicant submitting a paragraph IV certification must include a specific statement in the ANDA application that it will give such notice).

³⁶ Basically the purpose of the 45 day period is to allow the patent holder sufficient time to obtain a preliminary injunction.

³⁷ 35 U.S.C. §271(e)(2)(A). The infringing act is the filing of the certification.

II. PATENT PROTECTION FOR BRAND DRUGS

Patents are the very essence of the U.S. brand pharmaceutical industry. As the pharmaceutical industry continues to aggressively push the frontiers of medicine with new treatments and cures, stronger patent rights are vital to enable brand pharmaceutical firms to recoup more of their R&D dollars, thereby increasing incentives to invest in R&D. It is important for pharmaceutical companies to manage their patent process with the same discipline and effort that they manage their strategic and innovative processes. Patent management can range from unstructured and informed to disciplined and leveraged.

Since 1997 when direct-to-consumer advertising has been permitted in the United States, brand pharmaceutical companies have increasingly adopted the strategies and tactics of consumer goods manufacturers. That is, their goal is to establish a “personality” for a product, international recognition and consumer demand.³⁸ The point is to maximize profitability during the product life cycle. However, challenges such as parallel imports and compulsory licensing erode patent protections.

Whereas, in many industries webs of related patents surrounding critical technologies are obtained, in the pharmaceutical industry a single patent may be far more critical to a product’s success.

³⁸ See *Branding Goes Global*, 15 IN VIVO: THE BUSINESS AND MEDICINE REPORT, May 2001, at 60 (describing the catchy and informative message developed by Novartis AG for their new diabetes drug nateglinide, branded as Starlix[®] and the consumer product type handling of the antihistamine, Claritin[®])

A. Strategies for extending exclusivity

Various strategies for extending exclusivity for blockbuster drugs have evolved since the passage of Hatch-Waxman. One strategy involves “reverse” licensing payments from the brand to the generic not to market the generic version, thus delaying the initiation of the 180 day period.³⁹ If the 180 day exclusive period never begins, other generic companies cannot enter the market, giving an indefinite patent term to the pioneer drug. The Federal Trade Commission (FTC) stepped in and these and other types of agreements between pioneer and generic companies which occur in the litigation context must be submitted to FTC.⁴⁰ There is a trend toward “authorized generics” just prior to the 180 day exclusivity period essentially trumping the 180 day exclusivity. Brand companies via licensing or patent settlement agreements are specifically authorizing generic versions of their drugs to come to market. Similarly, the FTC has determined that “reverse payments” from the brand to generic company is illegal because the payment was made in consideration of the generic company agreeing to enter the market at a later date than it otherwise could have.⁴¹

³⁹ Federal Trade Commission, *GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION*, available at www.ftc.gov, July 2002, Chapter 1.

⁴⁰ *See, e.g.*, *FTC v. Hoechst Marion Roussel, Inc., Carderm Capital L.P. and Andrx Corp.*, Docket No. 9293 (consent order issued May 8, 2001) (FTC Commission Actions: May 11, 2001); *Schering-Plough Corp. Upsher-Smith laboratories, and American Home Products Corp.*, Docket No. 9297 (complaint issued April 2, 2001) (FTC Commission Actions: April 2, 2001).

⁴¹ *In re Schering Plough Corp.*, FTC, DKT No. 9297, 12/18/03 (currently being appealed to the U.S. Court of Appeals for the Eleventh Circuit).

1. New Orange Book Patents

The current method of choice for extending exclusivity is adding new patents to the Orange Book shortly before the other listed patents are about to expire.⁴² Some common types of patents which may be issued after FDA approval are those for revised formulations, new uses, new crystalline forms, metabolites or intermediates of the active ingredient. Obviously, the greater the number of Orange Books patents listed, the greater the hurdle for the ANDA applicant. The ANDA applicant must provide certifications to all listed patents that claim rights to the drug. The ANDA applicant who then files a Paragraph IV certification to this new patent, will in all likelihood be sued for patent infringement. The pioneer company will be entitled to another 30 month stay. Filing the Orange Book patents at month 29 of the first 30 month stay was common for a while.⁴³ This, however, depends on the Patent & Trademark Office as a patent may be listed in the Orange Book only within a 30 day period following its date of issue. By adding new patents to the Orange Book at the “right” time pioneer companies were enjoying multiple 30 month stays. The result was a *de facto* extension on the length of the patent term.⁴⁴

⁴² This is sometimes referred to as “late listing” or submarine patents.

⁴³ Because the new patents emerge just months before the original patents are due to expire. Also, companies can keep their patent position secret at the PTO by filing multiple extensions and continuation applications. When the patents are allowed they emerge like submarines. A pharmaceutical company has to list with FDA any new patent that covers its drugs within 30 days after issuance of the patent. Confusion has developed as to whether a patent was late-listed with regard to any given ANDA.

⁴⁴ Steve Lee, *Third Party Without Remedy in Orange Book Case. 4th Circuit Holds That FDA’s Refusal to List a Patent Was Not Arbitrary or Capricious*, Nat’l Law J., Nov. 11, 2002, at C6. (indicating that a patent could be extended indefinitely by listing a new patent every few years).

A prime example of the successful use of this strategy involved Diprivan injection where a change from a nonpreserved to an EDTA preserved formulation and a late listing of the patent to the preserved formulation significantly delayed generic versions. Another example that has been commonly used most recently is adding patents that change the crystalline form from anhydrous to a dihydrate form, which only differs in the water of hydration of the active ingredient.

Another example of the successful use of listing of additional patents involved paroxetine. The paroxetine litigation began in the early 1990s when SmithKline Beecham filed an NDA for Paxil, and identified U.S. Patent No. 4,721,723, which claimed the anhydrous form of the drug. The FDA approved this NDA in December 1992. In March 1998, Apotex filed an ANDA for a generic version, including a Paragraph IV certification for the '723 patent. SKB then filed a patent infringement suit in the Northern District of Illinois against Apotex within the 45 day period. That suit triggered the automatic 30 month stay, during which the FDA could not approve Apotex's ANDA. This stay expired November 2000.

In February and May 1999, after Apotex had filed its ANDA, SKB was awarded two additional patents claiming polymorphs. SKB then filed these patents with FDA for listing in the Orange Book. Because Apotex's ANDA was still pending, the FDA required it to file certifications for each of these patents. When Apotex filed paragraph IV certifications, it was used for infringement of these patents in the Eastern District of Pennsylvania. The FDA treated this lawsuit as triggering a second 30 month stay of approval of Apotex's ANDA, which expired in January 2002.

In February 2000, Apotex initiated an administrative petition with FDA

challenging its refusal to grant final approval of the ANDA. When the FDA failed to act on this claim, Apotex filed suit in the U.S. District Court for the District of Columbia. After this suit was filed 3 additional patents issued to SKB. SKB promptly submitted these patents to FDA for listing in the Orange Book, in response to which FDA required Apotex to file certifications for these patents, After Apotex filed paragraph IV certifications, SKB filed three additional infringement suits, all in the Eastern District of Pennsylvania. The FDA again treated each suit as giving rise to separate 30 month stays of approval to Apotex's ANDA.

The U.S. District Court for the District of Columbia dismissed Apotex's suit, whereupon it appealed to the Federal Circuit. On October 27, 2003, that court issued an extensive opinion which, *inter alia*, upheld the FDA's requirement for additional certifications after an ANDA is first filed, on the grounds that this practice was "consistent with the intention and does not violate any provision" of the Hatch-Waxman Act. Obviously, this is one of the cases that motivated the need to reform the practice of multiple 30 month stays.

2. Metabolite Patents

Another strategy for extending exclusivity involved patenting metabolites and listing them in the Orange Book, sometimes on the eve of patent expiration.⁴⁵ This strategy worked merely because the ensuing litigation itself was effective in preventing

⁴⁵ The "metabolite theory" which first surfaced in the mid-1980s, relies on the manufacturer's ability to identify and separately patent chemical compounds created *in vivo* when a drug is metabolized. With one or more metabolite patents in hand, the company's lawyers sue generic makers, contending that the knock-off companies seek to induce patients to unwittingly produce the metabolite in their bodies.

generic competition, as no Court actually upheld the “metabolite theory.” As Orange Book filings have listed more patents, the length of litigation has increased.

One example would be the metabolite patent for BuSpar, which was listed in the Orange Book one day before the expiration of buspirone’s exclusivity and later tossed out by a district court which held that the metabolite patent cannot be listed in the Orange Book because it does not claim the approved product.⁴⁶ Therefore, following the Court’s reasoning, a generic applicant cannot directly infringe but was contributing to infringement by selling the drug to patients who will metabolize it.

In *Schering v. Geneva Pharmaceuticals* the court recently held that a patent on a drug that does not explicitly describe a metabolite inherently discloses the metabolite if it teaches administration of the drug to the patient and it necessarily follows that the metabolite is formed.⁴⁷ As a result, the patent inherently anticipates claims directed to the metabolite in a patent application filed more than one year after issuance of the patent to the drug, even if the metabolite was not publicly known until after the filing of the metabolite application.⁴⁸

3. Polymorph Patents

Yet another strategy to postpone generic competition for old drugs involves the patenting of polymorphs. Polymorphs are different forms of the drug substance, such as a

⁴⁶ *Mylan Pharmaceuticals, Inc. v. Thompson*, 139 F. Supp. 2d 1,19-21 (D.D.C. 2001), *rev’d on other grounds*, 268 F.3d 1323 (Fed. Cir. 2001).

⁴⁷ 2003 WL 21767852 (Fed. Cir.).

⁴⁸ Mark J. Cohen, *A Change in Pharmaceutical Prosecution Practice*, 10 INTELL PROP TODAY, Oct. 2003, at 29.

different crystalline structure or hydration state; they manifest different x-ray diffraction patterns and are studied by x-ray diffraction.⁴⁹ They can be listed if the patent holder has in its files specified data showing that the polymorph would be considered the “same” (i.e., dissolution and bioavailability) as the approved ingredient for purposes of filing an ANDA.⁵⁰ Such patents may be listed in the Orange Book without actually being used in the commercial drug product. The District Court in *Zenith Labs v. Abbott Labs* upheld the listing of a polymorph for the hypertension drug, Hytrin.⁵¹ In these polymorph cases, it is often argued that the accused form converts into the claimed compound within the patient’s stomach.⁵²

Yet another strategy is the patenting of intermediates used in the production of an active ingredient. At least one district court found that an intermediate of a drug could be listed in the Orange Book, but the decision was based on the finding that the intermediate was actually a “component” of the drug rather than upon whether the intermediate compound “claimed the approved drug product.”⁵³

⁴⁹ See generally G.A. Stephenson, *Structure Determination From Conventional Powder Diffraction Data. Application to Hydrates, Hydrochloride Salts, and Metabolite Polymorphs*, 89 J. PHARM. SCI. 958, 966 (2000).

⁵⁰ Since FDA usually grants approval for only one polymorphic form of an active ingredient in a single NDA application, some argue that polymorphs are not part of the approved drug product and that additional patents for polymorphs should not be listed in the Orange Book. Others argue that since FDA will approve polymorphic generic formulations as bioequivalents of the patented drug they do claim the same drug and should be listed in the Orange Book. This argument is moot in view of the FDA Final Rule of 2003.

⁵¹ 1996 WL 33344963, at *10 (D.N.J. Aug. 7, 1996).

⁵² See, e.g., *Zenith Laboratories v. Bristol Myers Squibb*, 19 F.3d 1418, 30 U.S.P.Q.2d 1295 (CAFC 1994) (relying on the reverse doctrine of equivalents as an infringement defense. That is if the accused infringer can show the accused product is so far changed from the invention to function in a different way, then he may escape literal infringement; Lawrence B. Ebert, *Reverse Doctrine of Equivalents. Infringement Defense as to Drug Polymorphs?*, 8 INTELL. PROP. TODAY 26, 26 (2001).

⁵³ *Ben Venue Labs. v. Novartis Pharm. Corp.*, 10 F. Supp.2d 446, 454 (D.N.J. 1998).

This frivolous listing of patents with multiple 30 month stays was becoming a major barrier to generic drug entry. FDA only served a ministerial function in listing patents in the Orange Book.⁵⁴ The question remained should patent listing review be a function of FDA.⁵⁵

The decision in *Andrx Pharmaceuticals v. Biovail Corp.*⁵⁶ suggests that suits against FDA under the Administrative Procedures Act when FDA has improperly listed a patent is an appropriate mechanism to pursue.⁵⁷ However, since a court challenge under the FDC Act is not permitted, the ANDA applicant must survive an administrative challenge and subsequently an Administrative Procedures Act action to challenge Orange Book listings. If an ANDA filer challenges patents via a paragraph IV certification and claims to FDA that the patent has been improperly listed, FDA sends a letter to the patent holder, requesting that they re-affirm the appropriateness of listing the patent. If the patent holder does so, the inquiry is at an end, as FDA accepts the patent holder's assertion. Additionally, the decision in *Bristol-Myers Squibb Co. v. Mylan Pharmaceuticals Inc.* reflects that improper patent listing in the Orange Book may subject an NDA holder to enormous liability under antitrust laws. Some companies are already seeking delisting of certain patents to avoid getting hit with antitrust lawsuits from states, FTC and patients. In addition to suits against the FDA and/or the patent/NDA

⁵⁴ FDA refused to determine independently what use a patent covers and accepted at face value the use claimed by the patent holder. *See American Bioscience v. Thompson*, 269 F. 3d 1077, 1080 (D.C. Cir. 2002) (indicating that FDA accepts at face value the accuracy of the NDA holders patent assertions).

⁵⁵ See, e.g., Anon, *Patent Listing Review Should Be FDA Function, Rep. DeLauro Suggests*, F-D-C Reports, THE PINK SHEET, March 25, 2002, at p. 4.

⁵⁶ 276 F.3d 1368, 1373-1376 (Fed. Cir. 2002).

⁵⁷ *See In re Buspirone Patent Litigation and Buspirone Antitrust Litigation*. Southern District of New York; at <http://www.ftc.gov/os/2002/01/busparbrief.pdf>.

holder, a Citizen Petition may be filed. However, Orange Book listing is governed by the Federal Food Drug and Cosmetic Act, under which no private right of action exists.

As product patents that claim the drug in an NDA expire, patent infringement suits on “method” patents that claim methods of using a drug for a particular use are becoming more common.

Another strategy is line extensions, e.g., a new formulation or a comparable drug just prior to expiration of the patent. The strategy is to patent the new formulation or line extension so that it may be marketed to the current users.

Another strategy we see is that some companies conduct an additional study where they amend their labeling just before patent expiration, thereby requiring generic companies to conduct similar tests to prove bioavailability. A prime example of this tactic was the so-called applesauce test. With four months of patent coverage left an expensive test was conducted for Prilosec sprinkled on applesauce for patients who have difficulty swallowing capsules. When FDA accepted the study, the product labeling changed, which sour applied generic competition by raising the bar because they had to match the labeling.

The only method of use patents that should be listed in the Orange book are those pertaining to approved indications. However, we are also seeing patents listed for unapproved indications. In *Purepac Pharmaceutical Co. v. Thompson*⁵⁸ the issue was a patent listed for an unapproved use of the epilepsy drug, Neurontin® (gabapentin) which led to a dispute between the generic companies vying for the 180 day exclusivity period. Purepac had submitted a section viii statement for Warner Lambert’s U.S. Patent No.

⁵⁸ D.C. Cir., Nos 02-5410 and 03-5 121, Jan. 20,2004.

5,084,479 (hereinafter the '479 patent) directed to the use of gabapentin for neuromuscular diseases yet listed in the Orange Book. FDA refused to accept Purepac's ANDA unless the section viii statement was changed to a paragraph IV certification. A lower court ordered FDA to delist the '479 patent and awarded exclusivity to Purepac. The competing generic company alleged, although unsuccessfully, that Purepac was not the first generic applicant to submit a substantially complete ANDA.⁵⁹

Recent decisions in *Warner-Lambert v. Apotex*.⁶⁰ and *Allergan Inc. v. Alcon Labs*⁶¹ where courts have held that an ANDA applicant does not need to re-certify to a patent claiming unapproved uses, place limitations on a patentee's ability to assert off-label use patents in ANDA litigation under the theory of "induced infringement."⁶² In patent litigation related to unapproved uses, brand companies are arguing that the introduction of a generic into the market could induce the generic's use for an unapproved indication, thereby causing infringement of the patent.⁶³

There is no dispute that the Hatch-Waxman Act has increased litigation. From 1984 to 1994, just 30 cases were decided. In 2001 alone, 32 cases were decided.⁶⁴ There

⁵⁹ See Dana A. Elfin, *Exclusivity Periods for Torpharm Rebuffed on Bid to Overturn FDA Decision Awarding Exclusivity to Purepac*, PHARM LAW & INDUST RPT, Vol. 2, No. 4, at 85, Jan. 23, 2004; see also <http://pacер.cadc.uscourts.gov/docs/common/opinions/200401/02-5410a.pdf>. (for the entire opinion).

⁶⁰ 316 F.3d 1348 (Fed. Cir. 2003).

⁶¹ 324 F.3d 1322 (Fed. Cir. 2003).

⁶² See *Purpac Pharm Co. v. Thompson*, 238 F. Supp. 2d 191 (D.D.C. 2002).

⁶³ See generally Sarah E. Eurek, *Hatch- Waxman Reform and Accelerated Market Entry of Generic Drugs. Is Faster Necessarily Better?*, 2003 DUKE L. & TECH. REV 18 (Aug 13, 2003) (for a clear and concise overview of the FDA Final Rule which became effective August 19, 2003).

⁶⁴ John Benassi & Jessica Wolff, *The Rise of Generic and "Branded Generics" Cause Dramatic Increase in Pharmaceutical Patent Litigation*, 11 INTELL. PROP TODAY 18, at 19, (Jan. 2004).

has also been a trend in appellate decisions. From 1989 to 1996, the Federal Circuit found in favor of the pioneer manufacturers most of the time, since 2001, the Federal Circuit has found clearly for the generic drug companies.⁶⁵

B. Legislative and regulatory changes in 2003

In 2002, the Federal Trade Commission put out a report citing some concerns it had about the brand industry attempting to extend patents on products.⁶⁶ According to the FTC study, there were cases involving several brand-name drugs between 1994 and 2000 in which repeated 30 month stays delayed access to generic drugs.⁶⁷

The pharmaceutical patent endgame has dramatically changed because of two legislative/regulatory changes. The first is FDA's Final Rule which went into effect on August 18, 2003 and curtailed the ability of brand names to extend patent life and has quickened the pace of entry of generic pharmaceuticals into the marketplace.⁶⁸ The

⁶⁵ *Id.*, at 19.

⁶⁶ Vonronica Kolidakis, *Generic Industry Waiting to See Effect of FDA Final Rule, Possible Legislation*, BNA PHARM. LAW & INDUST. , Vol. 1, No. 32, pp. 921, August 22, 2003.

⁶⁷ *Generic Drug Entry Prior to Patent Expiration*, Federal Trade Commission, July 2002. (reporting eight instances where late-listed patents resulted in multiple 30 month stays on ANDA approval); *see generally* A Review of the FTC Report: Before the Subcommittee on Health, Oct. 9, 2002 (statement of Honorable L. Crawford, Acting Commissioner, U.S. FDA).

⁶⁸ 68 Fed. Reg. 36675, June 18, 2003 (implementing regulations which were initially issued in 1994. FDA decided to implement the rule rather than wait to see what Congress would do with pending Medicare legislation. The Medicare legislation includes many of the FDA rule provisions). *See generally* Michelle Meadows, *Greater Access to Generic Drugs*, FDA CONSUMER, Sept-Oct 2003 (quoting the Health and Human Services Secretary Tommy G. Thompson that the new FDA rule is expected to save consumers \$35 billion over 10 years, as well as lower costs for state Medicaid programs and employer-provided coverage. To supplement the regulation, the FDA also launched an initiative called "Improving Access to Generic Drugs". The initiative involves revamping the FDA's review process to put generics into consumers' hands more quickly. President Bush's fiscal year 2004 budget request increases funding for the FDA's generic drug program by \$13 million, the largest ever for that program with the goal of speeding up generic drug reviews.

second legislative change is the Medicare Prescription Drug Improvement and Modernization Act (MPDIMA) of 2003⁶⁹ where provisions were also enacted closely mirroring the FDA's final rule and providing greater access to generic drugs.⁷⁰ Most recently, FDA has decided to repeal its final rule in favor of the MPDIMA. The effect is strict limits on the 30 month stay and clarification on the types of drug patents that can be listed in the Orange Book.

1. Limitations on 30 Month Stays

Under the new rule, brand manufacturers will no longer be able to receive multiple 30 month stays on the consideration of ANDAs while possible patent infringements are investigated. Only one 30 month stay is permitted for each ANDA or 505(b)(2) application (a 505(b)(2) application seeks approval of a new drug but in its report of safety and efficacy, at least some of the data relied upon come from studies conducted by third parties, not by, or on behalf of the applicant.); but there may be multiple ANDA applicants for one listed drug product.

Before this, an NDA holder could obtain multiple 30 month stays by listing additional patents after the first stay had been triggered. Since 1998 infringement suits have involved more patents per ANDA, resulting in multiple 30 month stays. The new rule eliminates the potential for "stacked" 30 month stays delaying generic entry. That is,

⁶⁹ P.L. No. 108-173. December 8, 2003. Sections 1101-1104 of the Act amends the Hatch Waxman Act, 21 U.S.C. §355.

⁷⁰ See 69 Fed. Reg. 9982, March 3, 2004 (where FDA sought comments until May 3, 2004 on how to best implement the Hatch-Waxman reforms contained in the new Medicare law). FDA has now decided to repeal the Final Rule rendering these comments moot.

the patent owner and the NDA holder could still seek judicial remedy through patent infringement litigation, including injunction under the Patent Act, the difference being this is without the benefit of multiple thirty month stays.

MPDIMA modifies the notice provision requirement for ANDA applicants. Under the changes an ANDA applicant who is amending an ANDA to include a new Paragraph certification must only notify the patent holder and NDA holder only if the original ANDA did not previously include a paragraph IV certification. If no notice is given, no additional stays on the ANDA can be asserted. Further, subsequent Paragraph IV certifications no longer trigger a new 45 day period within which the NDA holder may file suit.

The Medicare Amendments eliminate a portion of the notice requirement required by the ANDA applicant and sets time limits for other portions.⁷¹ Notice must be provided by generic applicants to NDA holders (1) if the paragraph IV Certification is in an ANDA, within 20 days of receiving notice from the FDA that the ANDA has been filed, or 2) if the paragraph IV certification is in an amendment or supplement to the ANDA, at such time the amendment or supplement is filed.⁷² However, to resolve infringement disputes prior to marketing, the ANDA applicant may voluntarily notify the NDA holder.⁷³ The NDA holder can then file a patent infringement suit at any time but such

⁷¹ 21 C.F.R. §§ 314.52(a)(3) and 314.95(a)(3).

⁷² 21 U.S.C. §355(j)(2)(B)(ii). *See* 21 C.F.R. § 314.96 (stating that an ANDA applicant may amend an unapproved ANDA by (1) revising existing information or (2) providing additional information, including additional paragraph IV certifications).

⁷³ This would be prudent because a generic firm would be unwilling to enter the market while the patent situation is in flux because of the large damage exposure.

suits will not result in a 30 month stay of FDA approval.⁷⁴ For example, Aventis recently filed suit against five generic companies for infringing Orange Book method of use patents on the antihistamine, Allegra® (fexofenadine). Five additional lawsuits were filed against the same five generic companies for infringement of non-Orange Book patents claiming fexofenadine intermediates and processes of making fexofenadine.⁷⁵

The 30 month stay is available only for patents listed by the innovator before the filing date of the ANDA. When a patent is listed after the filing of an ANDA but before approval of the ANDA, the 30 month stay provisions will be triggered if the ANDA applicant has amended the ANDA to include the certification, before the date that the application is determined to be substantially complete.

2. Clarification of Orange Book Patent Listing

The Medicare Amendments clarify the new vision of the types of patents that should - and should not- be submitted for listing in the Orange Book. With the amendments the only patents that are currently permitted in the Orange book are patents claiming either the “drug substance” (active ingredient) of the drug that is the subject of the NDA; patents claiming the “drug product” (formulation and composition) that is the subject of the NDA; product-by-process patents where claim is made to a drug that is made by a particular process; and method-of-use patents. Product-by-process patents are

⁷⁴ Deborah Shelton, FDA ‘s Final Hatch-Waxman Regulations, at <http://www.arentfox.com/publications/alerts/alerts/2003.html> visited December 24, 2003.

⁷⁵ Aventis Pharmaceuticals Inc. v. Dr. Reddy’s Laboratories, Ltd., D.N.J., No. 2:04-CV-01075-JAG-GDH, filed 3/5/04.

required to be listed only if the product can be identified as novel.⁷⁶ Previously, an NDA applicant would merely file a declaration statement that the patent covers either the formulation, composition or method of use.⁷⁷ This has now been replaced with a multi-page “checklist” type declaration form which requires identification of the relevant patent claims.⁷⁸

The NDA holder must now submit information on each patent that claims the drug product (active ingredient) (including polymorphs), drug substance (formulation/composition), or a method of using the drug that is the subject of the NDA, amendment, or supplement and with respect to which a claim of patent infringement could be asserted. That is, patents having claims to methods of using that are not in the labeling must not be listed. To safeguard against listing inappropriately, the specific method of use claims and the labeling language related to that claim must be identified in the declaration forms. Additionally, the Medicare Prescription Drug Improvement and Modernization Act of 2003 permits the applicant to counterclaim for an order requiring the patent holder to “correct or delete” the patent information submitted by the holder. The ANDA applicant may seek a de-listing order “on the ground that the patent does not claim either: the drug for which the application was approved, or an approved method of

⁷⁶ A product-by-process patents claim a product by describing or listing process steps to wholly or partially define the claimed product. The patented, novel invention is the product and not the process that is used to make the product.

⁷⁷ 21 C.F.R. §314.53(c)(2)(i) (pertaining to the declaration that must be submitted). The declaration providing that: “The undersigned declares that Patent No. _____ covers the formulation, composition, and/or method of use of (name of drug product). This product is (currently approved under Section 505 of the FDCA) [or] (the subject of this application for which approval is being sought).” It is believed that requiring the NDA holder to submit a more detailed declaration in order to list a patent in the Orange Book will prevent improper listing.

⁷⁸ False statements regarding the patents submitted to FDA could lead to criminal charges.

using the drug.”⁷⁹

A major change is that polymorph patents must now be listed. Specifically, if a patent claims a polymorph of the active ingredient in the drug product that is the subject of an NDA, and that polymorph is demonstrated to be the “same” as that active ingredient, the patent should be listed. However, the FDA final rule requires that the polymorph form claimed by the patent submitted for listing satisfy specific testing that demonstrates “sameness”, particularly with respect to dissolution, solubility, and bioavailability. What effect does Orange Book listing of polymorph patents have? Possibly it makes it more difficult for generic companies to design around existing patents.

Process patents, i.e. those that claim the process used in manufacture of the drug product, packaging patents, metabolite patents, and patents claiming intermediates are not listable in the Orange Book.⁸⁰ According to the FDA Rule “Because metabolites exist only after the approved drug has been broken down inside the body, a patent claiming a metabolite does not claim the approved drug.” The only circumstances where a metabolite-related patent may be listed is when it is in a method-of-use patent.⁸¹

⁷⁹ Significantly changing the law as previously no private cause of action existed under the FDCA. *See, e.g.* Mylan Pharmaceuticals v. Thompson, 268 F.3d 1323, 60 U.S.P.Q.2d 1576 (Fed. Cir. 2001) (*citing* 21 U.S.C. §337(a) (1994) that...”all such proceedings...shall be by and in the name of the United States; Andrx Pharmaceuticals v. Bioavail Corp. 276 F.3d 1368, 61 U.S.P.Q.2d 1414 (Fed. Cir. 2002) (finding that the proper for raising the issue of improper FDA conduct is the Administrative Procedures Act); 3M v. Barr Laboratories, Inc. 2002 U.S. App. LEXIS 8346 (May 1, 2002).

⁸⁰ The rationale for not listing intermediates is that intermediates as in-process materials and therefore, are not present in the finished drug product. Additionally, for packaging the exception is that patents claiming a container that is an integral part of the dosage form (e.g. pre-filled drug delivery systems) should be listed.

⁸¹ A metabolite patent would be listable if it meets all the requirements and claims an approved method of using an approved drug to administer a metabolite.

3. Declaratory Judgment

Another change is that the Medicare Rx Drug Improvement Act permits the ANDA applicant to file suit for declaratory judgment if (1) the 45 day period has expired without the patent owner suing for infringement of the patent for which it has received notice of a paragraph IV certification; and (2) if the paragraph IV certification asserts noninfringement, the notice must include an offer of confidential access to the ANDA for the purpose of determining whether an action for infringement should be filed.⁸² A declaratory judgment sought is that the patent is invalid or will not be infringed. The purpose of the new language regarding declaratory judgments is to permit a generic company to get an early ruling on the validity of the branded company's patent. A second purpose was to allay concerns about the Article III constitutionality of those provisions.⁸³ Article III requires a party to have standing to seek judicial determination of a dispute. Patents are presumed valid. It has been argued that the ability to challenge a patent merely because of Orange Book listing, without meeting the standing requirements of 28 U.S.C. § 2201, and without there being a case or controversy is contrary to law and constitutional requirements.

⁸² In other words, a generic applicant is permitted to bring a declaratory judgment action only if the generic applicant provides a "right of confidential access" to its ANDA.

⁸³ GOP Medicare Bill Reforms Law for Generic Drugs, 67 PATENT, TRADEMARK & COPYRIGHT 49, 50, Nov. 21, 2003; see generally Donna A. Elfin, *Hatch- Waxman Fix May Delay Market Entry of Generics*, *FTC Commissioner Leary Says*, PHARM LAW & INDUST, Vol. 2, No. 10, March 5, 2004, at 260 (*quoting* the FTC Commissioner Thomas B. Leary as predicting that the declaratory judgment may deter generic entry as entry companies would be unwilling to enter the market while the patent situation is influx).

4. Clarification of Paragraph IV Notice Requirements

The new legislation also makes refinements to the provisions relating to the 180 day exclusivity period. Specifically multiple companies are now eligible to qualify for the 180 day exclusivity if they all file their application on the first day of eligibility. “Shared exclusivity” refers to FDA awarding marketing approval, and the accompanying 180 days of exclusive generic marketing rights, to more than one manufacturer of a generic drug. Shared exclusivity encourages more manufacturers to develop generic drugs earlier, thus encouraging competition and providing earlier patent access. Previously, when different generic applicants had valid exclusivity claims on different patents for the same product, these competing claims for exclusivity would block each other so that no application could be approved.⁸⁴

One drawback is that there are often unforeseen impediments to bringing a product to market which have nothing to do with intentional anticompetitive behavior.

III. FUTURE DETERMINANTS OF PATENTING

A. Offensive patenting

Patent attorneys typically focus on issues of patentability- non-obvious subject

⁸⁴ FDA TALK PAPER, *Department of Justice Appeals Court Decision Regarding FDA’s Shared Exclusivity Determination for Generic Paroxetine Hydrochloride Tablets*, T04-04, Feb. 5, 2004; see FDA web site at <http://www.fda.gov/bbs/topics/NEWS/2004/new01030.html>. The date on which the first complete ANDA application is submitted to challenge a brand-name drug product is now disclosed on the FDA web site. However, the name of the generic company will not be disclosed.

matter, novelty, prior art and draft complex patents complete with technical jargon. Drug Regulatory Affairs professionals focus on drug safety and efficacy. For most pharmaceutical companies today, the only time the patent and regulatory departments ever seem to get together, other than company social events, is when a Hatch Waxman event occurs. Such events are the review of a generic drug applicant's certification of non-infringement, a patent term extension opportunity following approval of an NDA, or when a blockbuster drug is about to come off patent. Most often these cooperative events between patent attorneys and drug regulatory affairs take place long after the drug patents were prosecuted, when it is often too late to do more than react to unfolding events in the marketplace.

The trend now is “offensive patenting” with a shift toward more aggressive patent creation and prosecution, a more proactive strategy. Offensive patenting both encourages and orchestrates the creation of patentable technologies. Offensive patenting can best be accomplished by screening disclosures for quality and relevance together with periodic review by a multifunctional team to evaluate the technological, business and legal merits of the disclosure.

Offensive patenting has traditionally been used by brand companies. For the brand industry, this involves not only “harvesting” more patents from the same R&D which is known as “evergreening” or multiple patenting but it also may involve open publication as a spoiling mechanism prohibiting others from getting a patent.⁸⁵ “Patent

⁸⁵ Title 35 U.S.C. §102. Patent protection is not available if “the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States.” Unlike those countries that operate under an “absolute novelty” requirement, the U.S. offers a one year grace period for inventors to file a patent application following a public disclosure of the invention. Therefore, inventors who are barred from obtaining patent protection in other countries, may still be entitled to patent protection in the U.S.

stacking” or “evergreening” occurs where companies obtain multiple patents on various aspects of a drug, varying dosages and methods of use and staggering the time when they are applied for so that when one patent expires, others are still effective. There is a tendency to file every disclosure in an effort to grow the patent portfolio, avoid design around patents, and assist in cross-licensing negotiations.⁸⁶

Product clearance studies are an integral part of offensive patenting.

Pharmaceutical companies that utilize an offensive patenting strategy may have core competencies in hard-to-manufacture products, niche pharmaceuticals using innovative technologies (e.g. novel drug delivery technologies). An example of an innovative technology is a chronotherapeutic or time-release dosage form. Some companies are evolving toward branded products as they apply their patented technologies to both branded and generic products.⁸⁷ This patenting strategy involves applying improved manufacturing and formulation technologies to flawed pharmaceuticals, thereby producing improved reformulated proprietary products.⁸⁸ In some instances, in conduct which seems almost antithetical to the notion of “generic”, the generic company seeks new indications for those drugs, further benefiting from participating in established markets already penetrated by the brand.

Another offensive strategy particularly useful for generic manufacturers who

⁸⁶ *Orange Book Will Go to Daily Listings In April, FDA Official Buehler Tells GPhA*, BNA PHARM. LAW & INDUST. Vol. 2, No. 10, March 5, 2004, at 261. Daily Orange Book patent listings are now available from FDA. New search features will allow for searching by patent number, newly listed patents, and patent delistings. A draft guidance on Orange Book listing is currently under review at the FDA.

⁸⁷ Examples of generic companies that have entered the brand name area are Andrx, Barr, Mylan Laboratories, Schein Pharmaceuticals, and Teva.

⁸⁸ These improved drug delivery technologies require submission of a New Drug Application to obtain FDA approval prior to marketing.

cannot afford the costs associated with litigation is patent reexamination.⁸⁹ The PTO has stated that an intended aim of *inter partes* reexamination is to provide a viable alternative to the great cost and uncertainty of patent litigation. Via reexamination a patent may be challenged while simultaneously filing a paragraph IV certification. Any litigation will be stayed until the re-examination is resolved by the PTO.⁹⁰ The American Inventors Protection Act of 1999 made a number of changes to the Patent Act which pertain to reexamination of patents. For example, the Act permits *inter partes* reexamination practice⁷⁹ but retains the current *ex parte* reexamination practice.⁹¹ *Inter partes* reexamination must be sought by a third party and applies to patents issuing from original applications filed in the U.S. on or after November 29, 1999. The new procedure provides additional third party rights whereby the third party requester may appeal any proposed ground of rejection not adopted by the examiner (i.e., a final decision favorable to patentability).⁹² This appeal may be made to the Board of Patent Appeals and Interferences (BPAI). In the past, the third party requestor could not be a party to any

⁸⁹ Reexamination is a process by which the validity of an issued U.S. patent is reviewed by the Patent Office upon limited grounds, i.e. prior patents and printed publications. Any request for reexamination must include: 1) a statement pointing out each substantial new question of patentability (must be a new question rather than just a challenge of the sufficiency of the original disclosure); 2) identification of every claim for which reexamination is sought, and a detailed explanation applying the art to the claims; 3) a copy of every patent or publication relied upon; 4) a copy of the specification and claims in cut up form; and 5) a certificate that the patent owner has been served ("Certificate of Service"). Anyone can file a request for reexamination, including the owner of the patent.

⁹⁰ See e.g., *Infringement Suit Against Atrix Labs Stayed While PTO Re-Examines Patent at Issue*, PHARM LAW & INDUST., Vol. 2, No. 11, March 12, 2004 at 286; *Tap Pharmaceuticals Products Inc., v. Atrix Labs, Inc.*, N.D. Ill., No.03-CV-7822, order granting stay 03/03/04. The reason for the stay of the litigation is to ensure that resources are not spent on prosecuting patent claims that may eventually be invalidated or changed by the PTO.

⁹¹ 35 U.S.C. §311-318 and 37 CFR 1.902-1.997.

⁹² 35 U.S.C. §302-307 and 37 CFR 1.510-1.570. While the examination is public, in the past third parties who initiated reexamination could not participate. Access to information submitted is available and this access goes right through to appeal on the part of the patent owner.

patent owner appeal to the BPAI. The third party requestor may now be so involved.⁹³ However, third party requesters may not appeal BPAI decisions to the courts.⁹⁴ Under the new procedures, if a final court or *inter partes* reexamination decision is favorable to patentability of a claim, the party opponent may not request or maintain an *inter partes* reexamination on such claim on the basis of issues raised or that could have been raised in the action or reexamination. *Inter partes* reexamination may, however, be requested based on newly discovered prior art unavailable to the third party requestor and the USPTO at the time of the *inter partes* reexamination. Further, a third party requestor (after order) is estopped from later asserting in any civil action the invalidity of any claim finally determined to be patentable on any ground the third party requestor raised or could have raised in the *inter partes* reexamination. Any party who requests *inter partes* reexamination is estopped from later challenging in a civil action any fact determined in a prior *inter partes* reexamination.⁹⁵

B. Defensive patenting

1. Narrowing in patent claim construction

Another trend at least for smaller startup pharmaceutical brand companies involves “defensive patenting”. Defensive patenting centers around internally developed technologies which are considered the crown jewels of the company. Patents are

⁹³ See 35 U.S.C. §315(b)(2). This appeal may be made to the Board of Patent Appeals and Interferences.

⁹⁴ 35 U.S.C. §134 (c).

⁹⁵ Except with respect to a fact determination later proved erroneous based on information unavailable at the time of the *inter partes* reexamination decision.

considered mainly as defensive tools. Here the patenting strategy is to develop a stronger patent portfolio to help the company defend itself against predatory competitors and to open cross-licensing opportunities. Firms which use defensive patenting may or may not have a proactive strategy to exploit the revenue generation potential of their patents. Pharmaceutical companies with defensive patenting strategies may realize the strategic significance of patent creation and protection but high enforcement costs continue to discourage such companies from aggressively enforcing their patent rights. They regard patent management expenses as overhead to be minimized rather than as a revenue generating exercise.

Pharmaceutical companies with defensive patenting strategies try to develop stronger, not necessarily more prolific, patent portfolios in order to defend against predatory competitors. High patent enforcement costs force these companies to regard patent management expenses as overheads to be minimized rather than as a revenue-generating mechanism.

“Strategic patenting” stems from the contractual view of property rights and the fact that stronger patents may increase incentives of firms to patent for reasons other than the traditional incentives provided by the patent system. Optimal strategies clearly depend on immediate and long range goals, needs, and opportunities. Many generic companies have R&D units working to diversify into new dosage forms, new therapeutic categories, and non-traditional products and are actively pursuing NDA filings and commercial agreements with brand pharmaceutical companies. These companies may have well defined processes for documenting inventions, writing invention disclosures, and deciding which disclosures should be filed as patent applications.

IV. CONCLUSIONS

Over the next 3 years, about 200 pharmaceutical patents are set to expire. It has been stated that the savings to employer health plans, state Medicaid programs, and to seniors from accelerated generic drug approval will amount to over \$3 billion a year.⁹⁶

The result of these new industry dynamics is new collaborative business relationships and strategic alliances as well as fierce competition between pharmaceutical manufacturers. However, the generic and brand industry are currently under scrutiny for possible antitrust violations.

For brand companies, a global strategy for the increasingly interconnected world pharmaceutical market is to build a brand early on that establishes a common world-wide identity. This adds to the risks and costs of bringing new medicines to market, and significantly alters the competitive landscape.⁹⁷ Branding is going global and brand companies are open to co-promotion partners. This is occurring just as generic companies are entering the foray into the world of brand pharmaceuticals.

A unique hybrid of FDC and patent law is being carved from recent CAFC decisions.⁹⁸ There has been an alteration of patenting strategies for both brand and

⁹⁶ See generally Justine Cannistra, *Has President Bush Found a Patently Obvious Solution?*, PHARM TODAY, Dec. 2002, at 13.

⁹⁷ See Ralph G. Schroeder & Paul Papas, *Protecting the Balance of Hatch- Waxman: Understanding the Industry's New Dynamics for the 21st Century*, 56 FOOD DRUG J.L. 19 (2001).

⁹⁸ See generally, Rebecca Eisenberg, *The Shifting Functional Balance of Patent and Drug Regulations*, 19 HEALTH AFFAIRS 119-35 (2001).

generic pharmaceutical companies. Additionally, FDA's newly issued amendments to Hatch Waxman will have far reaching effects on patenting of pharmaceuticals.⁹⁹ The new pharmaceutical patent end game with its newly written rules which significantly amend the Hatch-Waxman Act consists of an intellectual property strategy that looks at problems associated with the end of the patent life from the day the patent is first filed.

A forward looking Hatch-Waxman strategy during the patent prosecution and claims drafting process and a better understanding of how Hatch-Waxman integrates drug patent and regulatory policies is necessary for helping both patent attorneys and regulatory professionals better strategize, at much earlier stages, how to deal with drug patent issues during the life cycle of the pharmaceutical product.

⁹⁹ *But see* IMS Health, 2003 (reporting that the price for generic drugs are increasing almost twice as fast as prices for brand name drugs possibly as a result of the consolidation of the generic drug industry and especially during the 6 month exclusivity period).